WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003348

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in electronic form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1, 2 and 4-10 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1, 2 and 4-10 in part

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2005/003348

Re Item II.

For the ternary complexes containing L-Lysine or L-arginine, the priority is not validly claimed. These ternary complexes were not mentioned in the priority document. As a consequence, document D20, cited below, can be used to assess inventive step in the sense of Article 33.3 PCT.

Re Item III.

In the present application, the International Searching Authority has restricted the search because of the following objections under Articles 5 and 6 PCT.

Present claims 1, 2 and 4-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples or specifically mentioned in the claims.

As it is not possible to form an opinion on unsearched subject-matter, the following must be limited accordingly.

Re Item V.

1. Reference is made to the following documents:

D1: WO 01/25217 A (HOFFMANN LA ROCHE) 12 April 2001 (2001-04-12) cited in the application

D2: WO 02/089824 A (HOFFMANN LA ROCHE ; FRIESS THOMAS (DE); SCHEUER WERNER (DE); KRELL HAN) 14 November 2002 (2002-11-14)

D3: WO 97/23465 A (BOEHRINGER MANNHEIM GMBH ; BOSIES ELMAR (DE); ESSWEIN ANGELIKA (DE); G) 3 July 1997 (1997-07-03) cited in the application

D4: GRAMS F et al: "PYRIMIDINE-2,4,6-TRIONES: A NEW EFFECTIVE AND SELECTIVE CLASS OF MATRIX METALLOPROTEINASE INHIBITORS"

BIOLOGICAL CHEMISTRY, Vol. 382, no. 8, August 2001 (2001-08), pages 1277-1285, XP008009641 ISSN: 1431-6730 Cited in the application

D5: FOLEY L H et al: "Novel 5,5-disubstituted pyrimidine-2,4,6-triones as selective MMP inhibitors" BIOORGANIC &; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 8, 23 April 2001 (2001-04-23), pages 969-972, XP002271775 ISSN: 0960-894X

D6: MASAHIKO SUZUKI et al: "A STUDY OF 1:1 PLUS 1:2 COMPLEXES BETWEEN BARBITURATE AND CYCLODEXTRIN USING THE FREEZING POINT DEPRESSION METHOD" CHEMICAL AND PHARMACEUTICAL BULLETIN, TOKYO, JP, vol. 41, no. 8, 1 August 1993 (1993-08-01), pages 1444-1447, XP000395593 ISSN: 0009-2363

D7: WO 00/40962 A (KOSAK KEN M) 13 July 2000 (2000-07-13)

D8: JOZSEF SZEJTLI: "CYCLODEXTRIN TECHNOLOGY" 1988, KLUWER ACADEMIC PUBLISHERS , DORDRECHT, NL , XP001194813

D9: KOIZUMI K et al: "[Comparison between interactions of alpha- and beta-cyclodextrin with barbituric acid derivatives]"
YAKUGAKU ZASSHI. JOURNAL OF THE PHARMACEUTICAL SOCIETY OF JAPAN. DEC 1974, vol. 94, no. 12, December 1974 (1974-12), pages 1515-1519, XP008034887 ISSN: 0031-6903

D10: LOUKAS YANNIS L: "Quantitative structure-binding relationships (QSBR) and artificial neural networks: Improved predictions in drug: Cyclodextrin inclusion complexes"
INTERNATIONAL JOURNAL OF PHARMACEUTICS (KIDLINGTON), vol. 226, no. 1-2, 11 September 2001 (2001-09-11), pages 207-211, XP002297397 ISSN: 0378-5173

D11: AKI HATSUMI et al: "Multimodal inclusion complexes between barbiturates and 2-hydroxypropyl-beta-cyclodextrin in aqueous solution: Isothermal titration microcalorimetry, 13C NMR spectrometry, and molecular dynamics simulation"
JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 90, no. 8, August 2001 (2001-08), pages 1186-1197, XP002297398 ISSN: 0022-3549

D12: LOPATA A et al: "Quantitative structure-stability relationships among inclusion complexes of cyclodextrins I: Barbituric acid derivatives" JOURNAL

OF PHARMACEUTICAL SCIENCES, vol. 74, no. 2, 1985, pages 211-213, XP001194803

D13: IWAOKU R et al: "Enhanced absorption of phenobarbital from suppositories containing phenobarbital-[beta]-cyclodextrin inclusion complex" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 4, 1982, pages 1416-1421, XP001194804

D14: CSABAI KATALIN et al: "Interaction of some barbituric acid derivatives with hydroxypropyl-beta-cyclodextrin" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 91, no. 1, 1993, pages 15-22, XP001202117 AMSTERDAM, NL ISSN: 0378-5173

D15: LEIN, MICHAEL et al: "The new synthetic matrix metalloproteinase inhibitor (roche 28-2653) reduces tumor growth and prolongs survival in a prostate cancer standard rat model" ONCOGENE, Vol. 21, no. 3, 2002, pages 2089-2096, XP002297399 ISSN: 0950-9232

D16: WO 00/37109 A (EUPHAR GROUP S.R.L; CORVI MORA, PAOLO) 29 June 2000 (2000-06-29)

D17: EP 1 018 340 A (TECNIMEDE-SOCIEDADE TECNICO-MEDICINAL, S.A) 12 July 2000 (2000-07-12)

D18: PIEL G et al: "Study of the influence of both cyclodextrins and L-Lysine on the aqueous solubility of nimesulide; isolation and characterization of nimesulide-L-Lysine-Cyclodextrin complexes" JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 86, no. 4, 1997, pages 475-486, XP002383359 ISSN: 0022-3549

D19: MURA P et al: "Ternary systems of naproxen with hydroxypropyl-[beta]-cyclodextrin and amino acids" INTERNATIONAL JOURNAL OF PHARMACEUTICS 24 JUL 2003 NETHERLANDS, vol. 260, no. 2, 24 July 2003 (2003-07-24), pages 293-302, XP002383360 ISSN: 0378-5173

D20: MURA P ET AL: "Solid-state characterization and dissolution properties of Naproxen-Arginine-Hydroxypropyl-[beta]-cyclodextrin ternary system" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 59, no. 1, 2005, pages 99-106, ISSN: 0939-6411

D1 is mentioned by the applicant for the synthesis of compounds II à V.

D2 is mentioned by the applicant for the synthesis of compound I.
D3 describes the structure-activity relationship of pyrimidine-triones for inhibiting MMPs.
D4 describes the anti-angiogenic activity of compound I of the present application, also known as RO 28-2653.
D5 describes the anti-angiogenic activity of the presently claimed compounds.
D6 describes complexes of barbiturates with alpha-cyclodextrin.
D7 claims several complexes de cyclodextrins. Among the complexed compounds, the barbiturates are mentioned (see claim 1).
D8 is a standard textbook on cyclodextrin complexes in pharmacy.
D9 describes complexes of other barbiturates with cyclodextrins.
D10 describes complexes of other barbiturates with cyclodextrins.
D11 describes complexes of other barbiturates with cyclodextrins, with the corresponding calculations and ^{13}C-NMR differences.
D12 describes complexes of other barbiturates (17) with cyclodextrins.
D13 describes complexes of other barbiturates with cyclodextrins, leading to enhanced absorption.
D14 describes complexes of other barbiturates (39) with hydroxypropyl-β-cyclodextrin. Study of the stability: the more the substituent is bulky, the more the complex is stable.
D15 describes the anti-prostate-cancer activity of RO 28-2653 (= compound I) with the corresponding MMPs mentioned.
Finally, documents D16 to D20 describe the synergistic effect of cyclodextrins and the amino acid lysine or arginine on the solubility of pharmaceutical agents.

2. Neither the binary complexes of the claimed trioxopyrimidines with cyclodextrin nor the ternary complexes of the claimed trioxopyrimidines with cyclodextrin and one of the amino acids L-lysine or L-arginine have been described in the prior art. Therefore, the present claims fulfil the requirements of Article 33.2 PCT for novelty.

3. The problem underlying the present application is to provide new compositions for administering the barbituric acid derivatives of formula **(I)**, known from documents **D1** to **D5** for their MMP inhibiting effects. As solution to this problem, the applicant proposes to complex the compounds of formula **(I)** with cyclodextrins. These complexes are, insofar as 5 representatives are concerned, prepared in the examples of the present application, and tested for their activity.

4. Although the presently claimed complexes are novel, the complexing of compounds with cyclodextrins is in itself not sufficient for establishing an inventive step in the sense of Article 33.3 PCT. Indeed, the basics of forming cyclodextrin complexes has been very well described in **D8**. In view of this document, the skilled person, when departing from any of **D1** to **D5** as closest prior art, would certainly (try to) apply the teachings of **D8** in order to solve the problem as mentioned.

5. Moreover, the skilled person would also know very well, that barbituric acid derivative complexing with cyclodextrins has been largely studied. Documents **D6**, **D7** and **D9** to **D15** have been cited to demonstrate this.

6. Special attention is drawn to document **D14**, which described the influence of the volume of the substituents in the pyrimidine-trione ring. Bulkier substituents are reported here to increase the stability of the complex formed. Therefore, this documents would perhaps even more incite the skilled person to use cyclodextrin complexing in order to improve the pharmaceutical properties of the compounds according to formula **(I)**. Again this implies, that the requirements of Article 33.3 PCT for inventive step are not met.

7. If the applicant were able to demonstrate an unexpected effect of the complexes claimed, it might be necessary to re-evaluate inventive step. Such a comparison should be made with the teaching of document **D14** in mind. Of course, since an unexpected effect cannot be extrapolated, it would then only be possible to acknowledge inventive step for those compounds / complexes, for which the unexpected effect has actually been demonstrated. At the present stage, no data are available to support this. Therefore, it is not possible to acknowledge an inventive step in the sense of Article 33.3 PCT.

8. Similarly, the joint addition of a cyclodextrin and one of the amino acids lysine or arginine is known from documents D16 to D20 to synergistically increase the solubility of different pharmaceutical agents. Again, starting from any of D1 to D4 as closest prior art, the skilled person would need no inventive skills to apply the teachings of one of the documents D16 to D20, in order to arrive at the ternary complexes presently

claimed. Therefore, these ternary complexes do not seem to fulfil the requirements of Article 33.3 PCT for inventive step, either.